Fine Needle Aspiration Cytology of Metastatic Plasmacytoid Urothelial Carcinoma- Report of Four Cases Including a Case of Mixed Plasmacytoid and Micropapillary Morphology

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Running Title: FNAC of Plasmacytoid Urothelial Carcinoma

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Abstract:

Objectives: To report a small series of fine-needle aspiration (FNA) cytology of plasmacytoid urothelial carcinoma (PVUC).

Study design: A computerized search of our laboratory information system was performed for the 5-year period (01/2008–01/2013) to identify all FNA cases in which the corresponding surgical pathology cases were diagnosed as PVUC.

Results: Four cases identified were from 2 men (ages 56 and 64) and 2 women (ages 72 and 46). The FNA smears demonstrated low to moderate cellularity and consisted predominantly of single and dyshesive, medium-sized tumor cells with eccentrically located nuclei and moderate abundant dense cytoplasm. The nuclei were oval with slightly irregular nuclear membranes and contained coarse granular chromatin with inconspicuous or small nucleoli. There was moderate nuclear variation in size. The nuclear to cytoplasmic ratio ranged from <1 to 3. Binucleation, cytoplasmic vacuoles, and perinuclear hof were occasionally seen.

Conclusions: FNA cytology of plasmacytoid urothelial carcinoma shares similar features with plasma cell neoplasms**,** lobular carcinoma of the breast, and signet ring cell carcinoma of the stomach. Being aware of the patient's clinical history and the potential diagnostic pitfall of this rare variant of urothelial carcinoma is important for an accurate diagnosis on FNA biopsy.

Key words: fine needle aspiration, plasmacytoid urothelial carcinoma, cytology, FNA

Introduction

The plasmacytoid variant of urothelial carcinoma (PVUC) is a rare and aggressive histologic variant of urothelial carcinoma. It has been recognized in the 2004 World Health Organization (WHO) classification of urothelial neoplasm.[1] It is usually diagnosed in advanced pathological stage showing metastases in 60% of patients and has lower survival rate than conventional urothelial carcinoma (UC).[2-4] Few reports on the urine cytologic findings of PVUC exist in the literature.[5-9] However there was only one case report of fine-needle aspiration (FNA) cytologic findings.[10] The diagnosis on FNA specimens can be challenging given its resemblance to plasma cells and typically without marked nuclear atypia. Recognition of this tumor is important, particularly at metastatic sites, since it may indicate disease recurrence typical of its aggressive behavior that may require a different therapeutic approach. We herein report our experiences with 4 FNA cases of PVUC including 1 with coexisting micropapillary urothelial carcinoma.

Case History

Case #1

A 71-year-old female presented with bilateral hydronephrosis. She was noted to have irregular bladder thickening, right side greater than left on CT scan. Cystectomy revealed a tumor involving the uterine wall, bilateral fallopian tubes and rectum (pT4, N0, M1). Thirteen months after receiving 9 cycles of chemotherapy, the tumor recurred in the perineal soft tissue diagnosed by FNA.

Case #2

A 55-year-old male presented with hematuria. He underwent a transurethral resection of bladder tumor that showed a high-grade urothelial carcinoma. The following cystectomy revealed PVUC

(95%) that had invaded perinephric fat, seminal vesicals and prostate and involved one of 46 regional lymph nodes (pT4, N1, Mx). Fourteen months after receiving multiple cycles of chemotherapy, a new lesion was found anterior to the left psoas near the left ureter. FNA confirmed metastatic urothelial carcinoma.

Case #3

A 46-year-old female presented with hematuria and a CT scan revealed irregular bladder thickening. Transurethral biopsy showed high-grade carcinoma with glandular differentiation and signet cell morphology. FNA of right iliac lymph node showed rare atypical cells highly suspicious for metastatic urothelial carcinoma. After 4 cycles of chemotherapy, the patient underwent radical cystectomy and showed PVUC (90%) with coexisting urothelial carcinoma in situ and metastasis to 2 of 25 regional lymph nodes (pT3a, N2, Mx). She was found 4 months later to have bone metastasis and peritoneal carcinomatosis.

Case #4

A 63-year-old male with hematuria and the transurethral biopsy revealed urothelial carcinoma, mixed micropapillary and plasmacytoid variant. The cystoprostatectomy showed tumor with mixed micropapillary and plasmacytoid pattern invading perivesical fat and adventitia of the left ureteral margin and involved 4 of 19 regional lymph nodes (pT4a, N2, Mx). Nine months after receiving chemotherapy, he was noted to have metastasis to left retroperitoneal lymph node that was diagnosed by FNA.

Materials and Methods

This study was approved by Indiana University Institutional Review Board. A computerized search of our laboratory information system was performed for the 5-year period (Jan 2008–Jan

2013) to identify all FNA cases in which the corresponding surgical pathology cases were diagnosed as PVUC. The reports, slides and related clinical histories were retrospectively reviewed. The patient's age, sex, metastatic tumor sites, tumor stage and histologic diagnoses were summarized in Table 1. The Papanicolaou-stained ethanol-fixed and Protol Hema 3-stained (Fisher Scientific, Kalamazoo, MI) air-dried direct smears from each case as well as the corresponding hematoxylin and eosin-stained slides from the corresponding surgical resection of the tumors were reviewed. Cytologic features including cellular cohesiveness, nuclear location, nuclear variation, chromatin, nuclear membrane, nucleoli, nucleus/cytoplasm ratio, cytoplasmic vacuole, perinuclear hof, binucleation and multinucleation were analyzed and tabulated (Table 2). Case 3 was stained with CK7, CK20, Ber-EP4, MOC31, CD138, Gata 3, calretinin, and D2-40. Additional stains p63, 34βE12, MUM1, ER and PR were retrospectively performed on the cell block of case 3 and sections from the corresponding surgical resection of tumor s in the urinary bladder.

Results

Cytologic Findings

The FNA cytology of PVUC showed low to moderate cellularity with predominantly single and dyshesive, medium-sized tumor cells. There was moderate nuclear variation in size. The oval nuclei were eccentrically located with slightly irregular nuclear membrane and contained coarse granular chromatin and inconspicuous or small nucleoli. The nuclear to cytoplasmic ratio ranged from low to intermediate. Occasional binucleation, cytoplasmic vacuoles and perinuclear hof were noted (Figure 1A, 1B). In case number 4, tightly cohesive clusters of tumor cells that representing micropapillary components of the tumor were also noted among individual

plasmacytoid tumor cells in the FNA smears of the metastatic retroperitoneal lymph nodes (Figure 2A).

Immunocytochemical stains were performed on the cell block of case 3 and the tumor cells expressed CK20, Ber-EP4 and MOC31, and focally expressed CK7 and 34βE12, but negative for CD138, p63, Gata3, MUM1, ER, PR, calretinin and D2-40. The corresponding bladder tumors of case 3 were positive for 34βE12, while negative for p63, MUM1. ER and PR.

Histologic Findings

The histology of Cases 1, 2, and 3 was similar. The tumor cells were relatively uniform, dyshesive with moderate abundant eosinophilic to amphophilic cytoplasm and eccentrically located nuclei with irregular nuclear membrane and indistinct nucleoli (Figure 1C). Foci of carcinoma in situ and a few malignant cells of signet ring cell type were also noted. In Case 4, there were mixtures of tumor cells with plasmacytoid and micropapillary features. Both patterns were admixed intimately throughout the tumor (Figure 2B).

Discussion:

PVUC is a rare and aggressive variant of urothelial carcinoma. Patients with PVUC who were diagnosed with a higher stage at cystectomy were more likely to have lymph node involvement, and positive surgical margins than patients with conventional UC. Median overall survival and disease-specific survival were 19 and 22 months for PVUC, respectively, which were significantly worse than patients with conventional UC. Plasmacytoid variant histology was also associated with a 2-fold increased adjusted risk of all-cause mortality.[14]

Fine needle aspiration is a popular, cost effective and safe procedure to obtain materials for the diagnosis of metastatic diseases. However, overall cytology experience with PVUC is

limited with only one recently reported case of FNA findings.[10] We describe herein the largest series of FNA cytology findings of metastatic PVUC. The cytologic direct smears in our series displayed low to intermediate cellularity composed of predominately medium-sized, dyshesive cells with the majority of the cells containing eccentrically located oval nuclei and slightly irregular nuclear membrane, coarse granular chromatin and inconspicuous or small nucleoli (Table 2). Binucleation, cytoplasmic vacuoles, signet ring cell feature and perinuclear hof were seen occasionally (< 5% of the cells). The nucleus to cytoplasmic ratio was low to intermediate (<1 to 3). The diagnosis on FNA is challenging because most cases will have low cellularity and demonstrating relatively low-grade nuclear atypia.

In our experience, pure PVUCs are rare. The majority of PVUCs will have a combination of conventional urothelial carcinoma, urothelial carcinoma in situ or other variant of urothelial carcinoma.[2-3] FNA cytology of the conventional urothelial carcinoma typically demonstrate higher grade of nuclear atypia with marked nuclear size variation, prominent nucleoli, more cohesive clusters and containing frequent cercariform cells. “Cercariform” cells containing unipolar cytoplasmic processes with non-tapered, flattened ends, were designated as such because of their resemblance to the cercaria of Schistosma.[12-13] In our series, components of conventional urothelial carcinoma were not present in the cytologic samples.

Tumor cells of PVUC also frequently have a monocyte-like or signet ring cell-like morphology, and are prone to misinterpretation as other neoplasms, especially in a limited sample, most commonly as plasma cell neoplasm, lobular carcinoma of the breast, signet ring cell carcinoma of the gastrointestinal tract, melanoma or neuroendocrine tumor. The correct diagnosis can be rendered by careful morphologic evaluation with correlation of clinical history. However, in a limited sample with pure plasmacytoid morphology or in patients with a history of

other malignancies, the use of immunohistochemical stains may be useful to achieve an accurate diagnosis. There have been previous series and case reports studying the immunohistochemical features of PVUC, but the staining results have been variable, especially for CK7, CK20, and CD138.[2,3] A concise panel including 34BE12, p63, MUM1, CDX2, estrogen receptor (ER), and progesterone receptor (PR) may aid in the distinction of PVUC from mimics. [15] In our experience, plasmacytoid UCs are consistently positive for 34BE12 and/or p63, while negative for MUM1, CDX2, ER, and PR. Lobular carcinoma of the breast is positive for ER and PR while negative for the rest. Plasma cell neoplasms are positive for MUM1 and negative for all others. Signet ring cell carcinomas of the gastrointestinal tract are positive for CDX2 and negative for the others. If melanoma and neuroendocrine tumors are in the differential diagnosis, markers such as chromogranin, synaptophysin, S100 and HMB45 should also be included. We have retrospectively stained this panel of immunostains on case 3. The immunostains cannot be retrospectively performed on other cases due to low cellularity in both direct smears and cell blocks. The tumor cells are positive for 34BE12 while negative for p63, MUM1, CDX2, ER, and PR which were demonstrated in both cell blocks of FNA and paraffin blocks of the original tumors in case 3. There are no specific immunohistochemical markers for the diagnosis of PVUC. The usually sensitive markers for diagnosis of conventional urothelial carcinoma such as Gata3 and p63 were negative in our case. Our case was positive for CK7 and 34BE12, which might be more sensitive markers in the diagnosis of metastatic PVUC. However a larger series of study for the application of the immunohistochemistry in the diagnosis of PVUC is needed.

Our series includes a case (case 4) of mixed plasmacytoid and micropapillary urothelial carcinoma where the histology demonstrated an even mixture of both plasmacytoid and micropapillary tumor components. The FNA cytology sampled from the retroperitoneal lymph

node showed metastatic dyshesive plasmacytoid tumor cells and cohesive groups of micropapillary carcinoma (Figure 2A and 2B). Both plasmacytoid and micropapillary urothelial carcinomas are rare, aggressive variants of urothelial carcinoma. Although urothelial carcinoma with combined plasmacytoid and micropapillary morphology in the same cystectomy specimens has been reported, our case is interesting in that both plasmacytoid and micropapillary components were also present in both primary and metastatic sites.[11]

FNA cytology of plasmacytoid urothelial carcinoma shares similar features with other neoplasms with plasmacytoid morphology. Being aware of the patient's clinical history and the potential diagnostic pitfall of this rare variant of urothelial carcinoma is important for an accurate diagnosis on FNA biopsy.

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Figure Legends

Figure 1. A, B) FNA cytology of plasmacytoid urothelial carcinoma: Single or loose aggregate of medium-sized tumor cells demonstrate a plasmacytoid appearance (A, Diff Quik, x600; B, Papanicolaou, x600). **C**) Histologic section of plasmacytoid urothelial carcinoma. Plasmacytoid tumor cells arrange in a single file pattern with rare signet ring cell morphology (H&E, x400).

Figure 2. A) FNA cytology of mixed plasmacytoid and micropapillary urothelial carcinoma: cohesive clusters of micropapillary carcinoma components noted with single plasmacytoid tumor cells in the background. (Papanicolaou, x400). **B)** Histology of mixed plasmacytoid and micropapillary urothelial carcinoma (H&E, x400).

Table 1. Clinical information

Case No	Age/Sex	FNA site	TNM stage	Histologic diagnosis	Corresponding surgery
1	72/F	Soft tissue, perineum	T4N0M1	Plasmacytoid UC, 100%	Cystectomy
2	56/M	Soft tissue, retroperitoneum	T4N1Mx	Plasmacytoid UC, 95% Classical UC, 5%	Cystectomy
3	46/F	Lymph node, right iliac	T3aN2Mx	Plasmacytoid UC, 90% Classical UC, 10%	Cystectomy
4	64/M	Lymph node, left retroperitoneum	T4aN2Mx	Mixed plasmacytoid (50%) and micropapillary UC (50%)	Cystectomy

Table 2. Cytologic features of plasmacytoid urothelial carcinoma

Cytologic features	Quantity	Observed in number of cases
Dyshesive single cells	>50% of cells	4
Eccentric nuclei	>50% of cells	4
Moderate nuclear variation	>50% of cells	4
Coarse nuclear chromatin	>50% of cells	4
Small or no nucleoli	>50% of cells	4
Mild irregular nuclear membrane	>50% of cells	4
Cytoplasmic vacuole	< 5%	4
Signet ring cell feature	< 5%	4
Cytoplasmic hof	< 5%	4
Binucleation	< 5%	4
Multinucleation	< 5%	4
Nucleus to cytoplasm ratio <1	>50% of cells	2
Nucleus to cytoplasm ratio 1-3	>50% of cells	2